Remarks

Reconsideration of the application is respectfully requested in view of the foregoing amendments and following remarks. Claims 1-23 were pending prior to the entry of this amendment. Claims 1-20, and 22 are amended herein. Claim 23 is allowed. Claim 21 is canceled herein. New claims 24-25 are added herein.

Support for the amendment of claims 1-19 can be found throughout the specification, such as on page 11, lines 1-22. Support for the additional amendment of claim 14 can be found throughout the specification such as on page 13, lines 7-26; page 18, lines 6-30; and page 11, lines 8-15. Support for the additional amendment of claims 18-19 can be found throughout the specification such as on page 13, lines 9-26 and page 2, lines 15-21. Support for the amendment of claim 16 and new claim 24 can be found throughout the specification, for example on page 10, lines 11-28. Support for new claim 25 can be found throughout the specification such as on page 4, lines 13-25.

Applicants believe no new matter is added herein. Reconsideration of the subject application is respectfully requested.

Maintained Rejections

Claims 1-3, 10, 17, 18, 20 and 21 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by O'Hare et al. (WO/97/05265). Applicants respectfully disagree with this rejection.

O'Hare et al. describe VP22 protein and the transportation of VP22 and another molecule from one cell to adjacent cells in a monolayer. The transport function of VP22 is localized to the 34 C-terminal amino acids. O'Hare et al. describe the production of fusion proteins including VP22 (or a protein with the transport function of VP22) linked to a heterologous protein, and VP22 linked to a nucleic acid, drug or marker (see page 4, lines 4-16). In several examples, the transport of the additional molecule is accomplished by transfecting (or introducing) VP22 into a host cell and separately introducing the heterologous protein, nucleic acid, drug or other molecule into the cells, and allowing VP22 to transport the molecule from one cell to another. Thus, the two molecules are associated in vivo and are not in any isolated aggregated form.

O'Hare et al. also describe the production of cell extracts including VP22 fused to a heterologous protein. These cell extracts are used to produce antibodies; particles of a specified size

are not isolated from these extracts. In addition, with regard to claim 18, O'Hare et al. do not describe mixing VP22 with any other molecule outside of the cell.

Thus, O'Hare et al. simply cannot be construed to disclose *isolated stable* aggregates including VP22 that are *0.1 to 5 microns in size*, and O'Hare et al. do not anticipate claims 1-3, 10, 17-18 and 20-21 as amended. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-3, 15, 16, 18, 20 and 21 are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by O'Hare et al., (U.S. Patent No. 6,184,038, hereinafter "the '038 patent"). Applicants respectfully disagree with this rejection.

The '038 patent is the U.S. national phase of O'Hare et al. Thus, the detailed description of the '038 patent is identical to the detailed description of O'Hare et al.

The '038 patent describes VP22 protein and the transportation of VP22 and another molecule from one cell to adjacent cells in a monolayer. The transport function of VP22 is localized to the 34 C-terminal amino acids. The '038 patent describes the production of fusion proteins including VP22 (or a protein with the transport function of VP22) linked to a heterologous protein, and VP22 linked to a nucleic acid, drug or marker (see page 4, lines 4-16). In several examples, the transport of the additional molecule is accomplished by transfecting (or introducing) VP22 into a host cell and separately introducing the heterologous protein, nucleic acid, drug or other molecule into the cells, and allowing VP22 to transport the molecule from one cell to another. Thus, the two molecules are associated in vivo and are not in any isolated aggregated form. The '038 patent also describes the production of cell extracts including VP22 fused to a heterologous protein. These cell extracts are used to produce antibodies; particles of a specified size are not isolated from these extracts. In addition, with regard to claim 18, the '038 patent does not describe mixing VP22 with any other molecule outside of the cell.

Thus, the '038 patent simply cannot be construed to disclose *isolated stable* aggregates including VP22 that are *0.1 to 5 microns in size*. The "038 patent does not anticipate claims 1-3, 15-16, 18 and 20-21 as amended. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-22 are rejected under 35 U.S.C. § 103(a) as being allegedly being obvious over O'Hare et al. or the '038 patent in view of Hawley-Nelson et al., and Schwartz et al., the combination further in view of Moyer et al.

O'Hare et al. and the '038 patent are discussed above.

Hawley-Nelson et al. teaches that a peptide can be covalently coupled to a nucleic acid-binding group, cationic lipids and dendrimers and their use in transfection compositions. Inclusion of peptides or modified-peptides in transfection compositions or covalent attachment of peptides to transfection agents resulted in enhanced transfection efficiency.

Schwartz et al. teaches dimeric cationic lipids and aggregates of these cationic lipids with anionic lipids. These cationic lipids can be used for the delivery of molecules into cells.

Moyer et al. teaches the introduction of cleavable polypeptide linkers in fusion proteins.

As discussed above, O'Hare et al. do not teach the purification of stable aggregates of VP22 that are 0.1 to 5 microns is size, or that these aggregates could be used to increase the transport of another molecule into a cell. None of Hawley-Nelson et al., Schwartz et al. or Moyer et al. teach, or render obvious the purification of stable aggregates that include a polypeptide with the transport function of VP22, let alone the specifically claimed aggregates, such as those of 0.1 to 5 microns in size. Thus, claims 1-22 as amended are not obvious over O'Hare et al., alone or in combination with Hawley-Nelson et al., Schwartz et al. and /or Moyer et al.

Submitted herewith as Exhibit A is Normand et al., *J. Biol. Chem.* 276: 10542-15050, 2001, a post-filing date publication of the work of the Applicants. Normand et al. disclose that it was previously shown that cell extracts including VP22 fusion proteins could be used to achieve transport of the protein within cells of the monolayer (see page 12042, paragraph bridging the first and second column). However, Normand et al. disclose that there are unusual properties of isolated VP22/fluorescent oligodexoynucleotide (F-ODN) aggregates, namely that they remain stable in the cytoplasm and can be activated by light to allow F-ODN (and protein) to diffuse through the cell (see page 10542, second column.

Specifically, Normand et al. describe that the addition of VP22 and F-ODN at a 1:1 to 1:2 (ee page 15044) resulted in the production of uniform regular spherical particles of 0.3 to 1 μm in size (use

of lower, limiting amounts of VP22 did not result in particle formation). Normand et al. describe the unexpected properties of these particles, namely that they efficiently deliver the F-ODN to the cell (and the ODN is transported to the nucleus (see page 15045). Unexpectedly, a short burst of light such as from a microscope objective "somehow induce[d] the release of the F-ODN for the otherwise stable particles into the body of the cell" (seep age 15045, second column). Thus, Normand et al. describe an unexpectedly superior property of the isolated aggregates that include VP22, namely that that they can be treated with light to enhance delivery.

Hawley-Nelson et al. and Schwartz et al. teach the use of lipids, such as liposomes, for delivery of molecules to cells. The delivery of F-ODN using isolated aggregated compositions including VP22 was compared with liposome-mediated delivery (Lipofectin). The fluorescence of the F-ODN was used to measure ODN delivery. A much brighter and uniform staining was seen using isolated stable aggregates including VP22 (see page 15047, second column and Fig. 6). The use of isolated stable aggregates of VP22 allowed delivery of ODN to the nucleus over a period of several days after the initial incubation with the isolated aggregates. Normand et al. disclose the successful delivery of proteins in isolated aggregates of VP22 that have a particle size of 0.1 to 5 μm. Thus, Normand et al. document three unexpected superior properties of the claimed compositions: (1) the delivery of both proteins and nucleic acids in a single type of stable aggregate with VP22, (2) the extended delivery of a molecule over an extended time period; and (3) controlled delivery using light activation. This documentation of unexpectedly superior properties overcomes any *prima facie* case of obviousness based on O'Hare et al., the '038 patent, Hawley-Nelson et al., Schwartz et al. and/or Moyer et al.

In view of the above remarks, and the data presented in Normand et al., reconsideration and withdrawal of the rejection are respectfully requested.

Allowable Subject Matter

Claim 23 is free of the prior art of record

Request for Interview

Applicants believe the present application is ready for allowance, which action is requested. If any issues remain, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office Action in order to arrange a telephonic interview. As briefly discussed with Examiner Zara, it is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP § 713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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